

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION: NDA 20386/S017**

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**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

**Application Number: NDA 20386/S017**

**Trade Name: Cozaar 25 and 50 mg Tablets**

**Generic Name: (losartan potassium)**

**Sponsor: Merck & Co., Inc.**

**Approval Date: June 9, 1999**

**INDICATION: Provides for redesigned physician sample cartons for Cozaar (losartan potassium) 50 mg Tablets and Hyzaar (losartan potassium/hydrochlorothiazide) 50-12.5 and 100-25 mg Tablets.**

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number: NDA 20386/S017**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

NDA 20-386/S-017  
NDA 20-387/S-012

JUN 9 1999

Merck & Co., Inc.  
Attention: Jeffery R. White, M.D.  
Sumneytown Pike, P.O. Box 4  
BLA-20  
West Point, PA 19486

Dear Dr. White:

Please refer to your supplemental new drug applications dated January 18, 1999, received January 25, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cozaar (losartan potassium) 25 and 50 mg Tablets (NDA 20-386), and Hyzaar (losartan potassium/hydrochlorothiazide) 50-12.5 and 100-25 mg Tablets (NDA 20-387).

We acknowledge receipt of your submissions dated May 10, 1999.

These supplemental applications provide for redesigned physician sample cartons for Cozaar (losartan potassium) 50 mg Tablets and Hyzaar (losartan potassium/hydrochlorothiazide) 50-12.5 and 100-25 mg Tablets.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (sample cartons submitted May 10, 1999). Accordingly, these supplemental applications are approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Zelda McDonald  
Regulatory Health Project Manager  
(301) 594-5333

Sincerely yours,

/s/ 6/7/99  
Raymond J. Lipicky, M.D.  
Director  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20386/S017**

**FINAL PRINTED LABELING**

APPROVED

NDA 20-387



0018026

Patient \_\_\_\_\_  
 Physician \_\_\_\_\_  
 Date dispensed \_\_\_\_\_

Patient Instructions

**HYZAIR® 100/25**  
 (LOSARTAN POTASSIUM-  
 HYDROCHLOROTHIAZIDE TABLETS)

4RK 747

Complimentary • 6083

**HYZAIR® 100/25**  
 (LOSARTAN POTASSIUM-  
 HYDROCHLOROTHIAZIDE TABLETS)

4RK 747

**HYZAIR® 100/25**  
 (LOSARTAN POTASSIUM-  
 HYDROCHLOROTHIAZIDE TABLETS)

4RK 747

**HYZAIR® 100/25**  
 (LOSARTAN POTASSIUM-  
 HYDROCHLOROTHIAZIDE TABLETS)

4RK 747

Complimentary • 1 Bottle of 7 Tablets • No. 3793

**HYZAIR® 100/25**  
 (LOSARTAN POTASSIUM-  
 HYDROCHLOROTHIAZIDE TABLETS)

4RK 747



Store at 25° C (77° F);  
 excursions permitted to  
 15-30° C (59-86° F) [see USP  
 Controlled Room Temperature].  
 Keep container tightly closed.  
 Protect from light.

HYZAIR is a registered trademark of  
 E. I. du Pont de Nemours and Company, Wilmington, DE  
 9208100 Printed on Recycled Paperboard  
 8776/NO 30% Post-Consumer Content



Each tablet contains  
 100 mg losartan potassium and  
 25 mg hydrochlorothiazide.

**USUAL ADULT DOSAGE:**  
 See accompanying circular.  
 Package not child-resistant. Keep this  
 and all drugs out of reach of children.

Rx only  
 Manufactured by:  
**MERCK & CO., INC.**  
 West Point, PA 19380, USA  
 by:  
**DuPont Pharma**  
 Wilmington, DE 19880 USA

**HYZAIR® 100/25**  
 (LOSARTAN POTASSIUM-  
 HYDROCHLOROTHIAZIDE TABLETS)

4RK 747

67627

Lot \_\_\_\_\_  
 Exp. \_\_\_\_\_



9208100

APPROVED

JUN 9 1999

NDA 20-387

Complimentary • 1 Bottle of 21 Tablets • NDA 20-387

4RK111

**HYZAIR<sup>®</sup> 50/12.5**  
(LOSARTAN POTASSIUM-  
HYDROCHLOROTHIAZIDE TABLETS)

Each tablet contains  
50 mg losartan potassium and  
12.5 mg hydrochlorothiazide

USUAL ADULT DOSAGE:  
See accompanying circular.

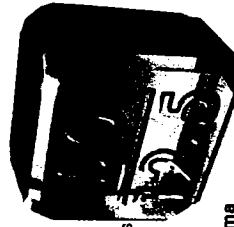
Package not child-resistant. Keep this  
and all drugs out of reach of children.

Rx only

Manuf. for:

**MERCK & CO., INC.**  
West Point, PA 19386, USA

by:  
**DuPont Pharma**  
Wilmington, DE 19880 USA



4RK111

**HYZAIR<sup>®</sup> 50/12.5**  
(LOSARTAN POTASSIUM-  
HYDROCHLOROTHIAZIDE TABLETS)

Lot

Exp.

67627

4RK111

**HYZAIR<sup>®</sup> 50/12.5**  
(LOSARTAN POTASSIUM-  
HYDROCHLOROTHIAZIDE TABLETS)

**50/12.5**



4RK111

**HYZAIR<sup>®</sup>**  
(LOSARTAN PO  
HYDROCHLORO

Patient Instructions

Physician

Patient

Date dispensed



8208000



**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20386/S017**

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**APPROVABLE LETTER**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 20-386/S-017

NDA 20-387/S-012

FEB 24 1999

Merck Research Laboratories  
Attention: Jeffrey R. White, M.D.  
Sumneytown Pike, P.O. Box 4  
BLA-25  
West Point, PA 19486

Dear Dr. White:

Please refer to your supplemental new drug applications dated January 18, 1999, received January 25, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cozaar (losartan potassium) 25 and 50 mg Tablets (NDA 20-386) and Hyzaar (losartan potassium/hydrochlorothiazide) 50-12.5 and 100-25 mg Tablets (NDA 20-387).

These supplemental applications provide for draft sample cartons for Cozaar (losartan potassium) 50 mg Tablets and for Hyzaar (losartan potassium/hydrochlorothiazide) 50-12.5 and 100-25 mg Tablets.

We have completed the review of these applications and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling (FPL) for the drug. The labeling should be identical in content to the sample cartons included in your January 18, 1999 submission.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 copies of the final printed labeling (to each application), ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed.

We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

NDA 20-386/S-017

NDA 20-387/S-012

Page 2

If you have any questions, please contact:

Ms. Kathleen Bongiovanni  
Regulatory Health Project Manager  
(301) 594-5334

Sincerely yours,

Raymond J. Lipicky, M.D.  
Director  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

cc:

Archival NDAs 20-386, 20-387

HFD-110/Div. Files

HFD-95/DDMS

DISTRICT OFFICE

HFD-110/K.Bongiovanni

sb/2/12/99;2/23/99

Initialed by: R Mittal/2/15/99

K Srinivasachar/2/16/99

A Proakis/2/16/99

C Resnick/2/18/99

K Knudsen/2/21/99

C Ganley/2/17/99

G Buehler for N Morgenstern/2/22/99

filename: 20386s017ae.doc

APPROVABLE (AE)

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20386/S017**

**ADMINISTRATIVE DOCUMENTS**

JUN 14 1999

CSO Review of Final Printed Carton Labeling  
NDA 20-386/S-017  
NDA 20-387/S-012

Date of Submissions: May 10, 1999

Date of Review: June 1, 1999

Applicant Name: Merck & Co., Inc.

Product Names: Cozaar (losartan potassium) 25 and 50 mg Tablets  
(NDA 20-386)

Hyzaar (losartan potassium/hydrochlorothiazide)  
50-12.5 and 100-25 mg Tablets  
(NDA 20-387)

Evaluation:

These submissions provide for final-printed physician sample cartons for Cozaar (losartan potassium) 50 mg Tablets and Hyzaar (losartan potassium/hydrochlorothiazide) 50-12.5 and 100-25 mg Tablets. I have reviewed the cartons and found them to be, as was requested in the February 24, 1999 approvable letter for these supplements, identical to the draft sample cartons submitted on January 18, 1999.

Recommendation:

Since the submitted final-printed physician sample cartons are identical to the January 18, 1999 submitted draft physician sample cartons, as was requested in the February 24, 1999 approvable letter for these supplements, I recommend that the Division issue an approval letter for these supplements.

/S/

Colleen LoCicero, CSO

cc: orig NDA 20-386  
orig NDA 20-387  
HFD-110  
HFD-110/LoCicero  
HFD-110/SBenton

FEB 24 1999

RHPM Review of Labeling

NDA: 20-386/SLR-017 Cozaar (losartan potassium) Tablets  
20-387/SLR-012 Hyzaar (losartan potassium/hydrochlorothiazide) Tablets

Date of submissions: January 18, 1999

Date of receipt: January 25, 1999

Applicant: Merck Research Laboratories

**Background:** Merck has submitted these supplements to provide for sample cartons (complimentary, each containing one bottle of 7 tablets) for Cozaar (losartan potassium) 50 mg Tablets and Hyzaar (losartan potassium/hydrochlorothiazide) 50-12.5 and 100-25 mg Tablets.

Our approvable letter for NDA 20-387/S-008, dated August 10, 1998, included the following:

"Please delete from the proprietary name in the package insert and all carton and container labeling. The is unnecessary and crowds an already cluttered abbreviation list. Listing the strengths (100/25) is adequate and succinctly provides a health-care practitioner with the essential information. Furthermore, by using the product is tied to a reference strength that may at some future time not be available. Also, terms like forte, and strong convey a therapeutic message of enhanced activity that may not be merited by the available data.

"Please delete the letters from the logo on the carton and container labels for all strengths of Hyzaar. has an established meaning for bioequivalence concerns as listed in the Orange Book, and its inclusion as part of a logo may render the labeling misleading."

**Review:** The three submitted draft sample cartons each include the proprietary and generic name, the tablet strength, the manufacturer, the sponsor, a place for lot number and expiration date, the storage statement, and the following statements:

- USUAL ADULT DOSAGE: See accompanying circular.
- Package not child-resistant. Keep this and all drugs out of reach of children.
- Cozaar or Hyzaar is a registered trademark of E.I. duPont de Nemours and Company, Wilmington, DE.
- Complimentary
- 1 Bottle of 7 Tablets

- Rx only
- Printed on Recycled Paperboard  
30% Post-Consumer Content

In addition, the Hyzaar cartons state either, "Each tablet contains 50 mg losartan potassium and 12.5 mg hydrochlorothiazide" or "Each tablet contains 100 mg losartan potassium and 25 mg hydrochlorothiazide."

Merck has removed the [redacted] from to logo from all cartons as we requested in the August 10, 1998 approvable letter for NDA 20-387/S-008.

**Recommendation:** I will prepare an approvable letter for these supplements for Dr. Lipicky's signature. These supplements ordinarily would fall under 21 CFR 314.70 (d), Changes described in the annual report, but since we asked for the revisions to the cartons, Merck submitted them in draft as labeling supplements.

**/S/**

Kathleen F. Bongiovanni

2-11-99

cc: NDA 20-386/S-017  
NDA 20-387/S-012  
HFD-110 (both)  
HF-2/MedWatch  
HFD-110/KBongiovanni  
HFD-110/SBenton

kb/2/11/99.

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20386/S017**

**CORRESPONDENCE**

Jeffery R. White, M.D.  
Director  
Regulatory Affairs

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Merck & Co., Inc.  
P.O. Box 4, BLA-20  
West Point PA 19486  
Tel 610 397 3180  
215 652 5000  
Fax 610 397 2516  
Email jeffery\_white@merck.com

ORIGINAL

May 10, 1999



Raymond J. Lipicky, M.D., Director  
Division of Cardio-Renal Drug Products  
HFD-110, Room 16B-45  
Office of Drug Evaluation I (CDER)  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

SLR-012  
(AE)

**NDA 20-387/S-012: HYZAAR™ Tablets (Losartan Potassium/HCTZ)  
Final Printed Labeling**

Reference is made to the above referenced Supplemental New Drug Application dated January 18, 1999 and to the Agency's Approvable letter dated February 24, 1999. This supplement provided for redesign of physician sample cartons for HYZAAR™ Tablets. Reference is also made to the Agency's August 10, 1998 letter in which this redesign was requested. Included with this submission, as requested in the February 24, 1999 letter, are 20 copies of each of the final printed labeling.

Enclosed:

1. Sample Carton for 100-25 mg Tablet
2. Sample Carton for 50-12.5 mg Tablet

Questions concerning this supplement should be directed to Jeffery R. White, M.D., (610-397-3180) or, in my absence, to Larry P. Bell, M.D. (610-397-2310).



Sincerely,

A handwritten signature of Jeffery R. White.

Jeffery R. White, M.D.  
Director, Regulatory Affairs

Enclosures  
Certified No. P 967 685 399

q\ba\mk954/fpl\_

ORIGINAL

Jeffery R. White, M.D.  
Director  
Regulatory Affairs

ORIGINAL

Merck & Co., Inc.  
P.O. Box 4, BLA-20  
West Point PA 19486  
Tel 610 397 3180  
215 652 5000  
Fax 610 397 2516  
Email jeffery\_white@merck.com

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March 31, 1999

Raymond J. Lipicky, M.D., Director  
Division of Cardio-Renal Drug Products  
HFD-110, Room 16B-45  
Office of Drug Evaluation I (CDER)  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



~~SUPPL NEW CORRESP~~

SUC  
SLR-012

NDA 20-386/S-017: COZAAR™ Tablets (Losartan Potassium)  
NDA 20-387/S-012: HYZAAR™ Tablets (Losartan Potassium/HCTZ)

**Intent To Amend**

Please refer to the above referenced Supplemental New Drug Applications dated January 25, 1999, received January 25, 1999, and to the Agency's Approvable letter dated February 24, 1999.

In accordance with 21 CFR 314.110, we wish to notify the Agency of our intent to file an amendment to this supplemental application.

Questions concerning this supplement should be directed to Jeffery R. White, M.D., (610-397-3180) or, in my absence, to Larry P. Bell, M.D. (610-397-2310).

Sincerely,

A handwritten signature in dark ink, appearing to read 'Jeffery White'.

Jeffery R. White, M.D.  
Director, Regulatory Affairs

Certified No. P 967 685 347

q\ba\mk954\int\_amend

Jeffery R. White, M.D.  
Director  
Regulatory Affairs

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Merck & Co., Inc.  
P.O. Box 4, BLA-20  
West Point PA 19486  
Tel 610 397 3180  
215 652 5000  
Fax 610 397 2516  
Email jeffery\_white@merck.com

**ORIGINAL**

NDA NO. 20-387 REF. NO. 012

NDA SUPPL FOR SLR



Raymond J. Lipicky, M.D., Director  
Division of Cardio-Renal Drug Products  
HFD-110, Room 16B-45  
Office of Drug Evaluation I (CDER)  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



NDA 20-387: HYZAAR™ Tablets  
(Losartan Potassium/Hydrochlorothiazide)

**DRAFT LABELING**

Dear Dr. Lipicky:

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act and in accordance with 21 CFR 314.70(c)(2), we submit a supplement to NDA 20-387 FOR APPROVAL. Reference is made to the Agency's approvable letter for HYZAAR™ 100-25 mg strength of August 10, 1998. In the August 10, 1998 approvable letter, the Agency requested deletion of \_\_\_\_\_ from all carton and container labeling.

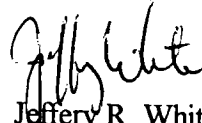
Reference is also made to the submission of September 11, 1998 in which final printed labeling, including a temporary 30 tablet unit of use HYZAAR™ 100-25 physician sample, was provided. With the present submission, Merck is submitting redesigned physician sample cartons for both strengths of HYZAAR™. As requested, the \_\_\_\_\_ have been removed from carton and container labeling.

As indicated on the attached Form FDA 356h, we are providing draft labeling for approval for HYZAAR™ Tablets. This submission consists of draft labeling of sample carton for the 50-12.5 mg tablet (Tab 1) and sample carton for the 100-25 mg carton (Tab 2). In accordance with the Food and Drug Administration Modernization and Accountability Act of 1997, no fee is required for this supplemental application.

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a (k) (1)], we hereby certify that, in connection with this application, Merck & Co., Inc. did not and will not use in any capacity the services of any person debarred under subsections 306 (a) or (b) of the Act.

We consider the filing of this Supplemental New Drug Application to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc. Please direct questions or need for additional information to Jeffery R. White, M.D. (610/397-3180) or, in my absence, Larry P. Bell, M.D. (610/397-2310).

Sincerely,



Jeffery R. White, M.D.  
Director, Regulatory Affairs

Attachments: Mounted Proofs of Sample Cartons For the 50-12.5 mg Tablet  
Mounted Proofs of Sample Cartons For the 100-25 mg Tablet

Certified No: P 967 671 287

Q:SELIGA/GINNY/LETTERS/20387DL